



Why Exercise is Good for You (EXGENESIS Project)



According to estimates by the International Diabetes Federation, 285 million adults worldwide have diabetes and, if current trends continue, this will rise to 440 million (7.8% of population) by 2030. The cost of treating diabetes worldwide is estimated at US \$375 billion annually, projected to rise to \$490 billion by 2030. Type 2 diabetes accounts for more than 90% of all cases, and a key factor in its increase in prevalence is increasing obesity (the risk of developing type 2 diabetes being about 20-fold higher in an obese rather than a lean individual). We believe that lack of opportunities for physical activity in the urban environment is a major factor causing this increase, and that the design of cities and their infrastructure need to take this into account.

Background

What is the cause of this epidemic of obesity and diabetes, and can be anything be done about it?

The partners in the EXGENESIS project, an Integrated Project in European Research Framework Programme 6 of the European Commission (2005-2009), believe that the problem is caused by increasing adoption of an urban lifestyle, characterized by lack of physical activity and constant availability of "fast food". These harmful environmental influences also interact with underlying genetic factors. The consortium, co-ordinated by Professor Grahame Hardie of the University of Dundee, Scotland, had 27 partners spread across 13 EU member states.

Aims

- to discover the mechanisms underlying the health benefits of exercise
- to identify signalling pathways and myokines causing metabolic changes during exercise
- to identify genetic and environmental factors that increase the risk of developing diabetes, especially during periods of physical inactivity

Results

EXGENESIS has:

- identified key signalling pathways that mediate the effects of exercise, especially the AMP-activated protein kinase (AMPK)
- found that AMPK is responsible for many of the metabolic changes during acute exercise, as well as the longer-term adaptations that occur in response to exercise training
- shown that the drug metformin, prescribed to 120 million patients with type 2 diabetes worldwide, works by activating AMPK indirectly, via inhibition of mitochondrial function
- established how AMP binds to AMPK, which will aid in the design of drugs that activate it directly



- identified several new *myokines*, molecules released by muscle that modulate metabolism in other organs, so that the health benefits of exercise may not just be confined to the muscle itself
- shown that supervised exercise sessions in middle-aged people at risk of developing diabetes have potential benefits not only on metabolism, but also on mental ability
- shown that volunteers who were confined to bed for nine days developed adverse metabolic changes, and that these effects could be more severe in high risk groups (first degree relatives of type 2 diabetic subjects, and individuals born with low birth weight)
- shown that even moderate reductions in physical activity, from 10,000 to 1,500 steps per day, in fit volunteers caused measurable insulin resistance, and increased abdominal fat, within 2 weeks
- identified a number of new genetic variants that increase the risk of developing diabetes

Impact

Work on the physiological role of AMP-activated protein kinase in muscle, and its structure and regulation, should aid in the design of new drugs that cause direct activation and thus avoid the side effects of indirect activators like metformin. Identification of myokines that transmit effects of exercise to organs other than muscle may eventually suggest new avenues for drug development. Our studies of physical inactivity revealed that even a moderate reduction in activity, to levels common in modern urban societies, has adverse metabolic effects, and that these can be greater in high risk individuals. Identification of new genetic variants that increase the risk of type 2 diabetes may ultimately allow targeting of exercise interventions to high-risk individuals.

For more information, please visit the website: www.dundee.ac.uk/lifesciences/exgenesis/

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